In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 09-489V

Filed: May 31, 2016

DULCE and SEAN REILLY, parents and natural guardians of E.R., a minor, Petitioners, v. SECRETARY OF HEALTH AND HUMAN SERVICES Respondent.	**TO BE PUBLISHED** Special Master Hamilton-Fieldman Vaccine Act Entitlement; Causation-in-Fact; Diphteria-Tetanus-Acellular-Pertussis ("DTaP") Vaccine; Infantile Spasms; Two-Hit Theory

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Ryan D. Pyles, United States Department of Justice, Washington, DC, for Respondent.

RULING ON ENTITLEMENT

This is an action in which the Petitioners, Dulce and Sean Reilly,[1] seek an award under the National Vaccine Injury Compensation Program (hereinafter "the Program"),[2] on behalf of their minor son, E.R., who suffered from "encephalopathy and intractable seizures"[3] allegedly caused-in-fact by his receipt of the Diphtheria-Tetanus-Pertussis ("DTaP" or "DPT")

[1] The Petition was filed naming only Dulce Reilly as Petitioner. The caption was amended on May 14, 2013, to reflect that both of E.R.'s parents are Petitioners. Order (May 14, 2013), ECF No. 73. For ease of reference, they are referred to as Petitioners throughout this decision.

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-1 to -34 (2012) (hereinafter "the Act").

[3] These were the injuries originally alleged in the Petition. In their pre- and post-hearing briefing, Petitioners allege that E.R.'s injury is a "seizure disorder."

vaccination,[4] which was administered on June 21, 2007. Pet. at 1, ECF No. 1. For the reasons set forth below, the undersigned concludes that Petitioners have met their burden of proof under the Act and *Althen v. Sec'y of HHS*, 418 F.3d 1274 (Fed. Cir. 2005), and are therefore entitled to a Program award.

I. FACTUAL BACKGROUND

E.R. was born on December 15, 2006. Pet'rs' Ex. 3 at 1.[5] E.R.'s mother had been admitted to the hospital at 37 and 1/7 weeks' gestation "for induction due to worsening ulcerative colitis." Pet'rs' Ex. 2 at 6. Her pregnancy had "been complicated by A2 gestational diabetes mellitus," and "she also had a history of malignant hyperhermia."[6] *Id.* Delivery, however, was "uncomplicated." *Id*. E.R. received a Hepatitis B vaccination at the hospital and was discharged after two days. *Id*. E.R. received pediatric care at Cape Fear Pediatrics. *See generally* Pet'rs' Ex. 4.

On February 15, 2007, E.R. was diagnosed with an acute upper respiratory infection. *Id.* at 81. He received the DTaP (as a component of the Pediarix) and pneumococcal conjugate ("Prevnar") vaccines at this appointment. *Id.* at 81, 95. E.R. had well-child examinations on February 28 and March 20, 2007. *Id.* at 80. During these examinations, E.R. was diagnosed with "[a]cute suppurative otitis media," "vomiting," and a "viral syndrome." *Id.* On April 16,

[4] The DTaP vaccination administered on June 21, 2007 was a component of the Pediarix vaccination which was administered to E.R. as part of his routine childhood vaccinations. *See* Pet'rs' Ex. 3 at 81, 95. Pediarix is a vaccine "indicated for active immunization against diphtheria, tetanus, pertussis, infection caused by all known subtypes of hepatitis B virus, and poliomyelitis." *Pediarix: Product Overview*, gsksource, https://www.gsksource.com/pediarix (last visited May 30, 2016). Pediarix is a combination vaccine, containing diphtheria, tetanus toxoids, acellular pertussis, hepatitis B (recombinant), and inactivated poliovirus. Pediarix, *Dorland's Illustrated Med. Dictionary* (32nd ed. 2012) (hereinafter "*Dorland's*"). Pediarix "is approved for "use as a three-dose series in infants born of hepatitis B surface antigen (HBsAg)-negative mothers." *Pediarix: Dosing and Administration*, gsksource, https://www.gsksource.com/pharma/content/gsk/source/us/en/brands/pediarix/pi/dosing.html (last visited May 30, 2016).

[5] Where no citation to the electronic docket is provided, the relevant filing was only made available via hard copy or compact disc.

[6] Malignant hypothermia is "a disease that causes a fast rise in body temperature and severe muscle contractions when someone with the disease gets general anesthesia. It is passed down through families." *Malignant Hyperthermia*, MedlinePlus, www.nlm.nih.gov/medlineplus/ency/article/001315.htm (last visited May 31, 2016).

2007, E.R. received one dose each of the rotavirus tetravalent and haemophilus influenza B vaccines, and second doses of the Pediarix and Prevnar vaccines. *Id.* at 79-80. During this April examination, E.R. was also diagnosed with esophageal reflux. *Id.* at 79. Thereafter, E.R. was seen on May 2 for an upper respiratory illness and was prescribed Zantac for gastroesophageal reflux disease. *Id.* at 79, 84.

E.R. next had a well-child visit on June 21, 2007. *Id.* at 76. E.R.'s mother reported that E.R. had not been "eating well," was "pulling at [his] ears," and was "more fussy than usual." *Id.* at 77. It was noted that prior to this visit, E.R. had been "very upset" and "irritable" and had "a mild fever." Pet'rs' Ex. 3 at 107. E.R. received third doses of the Pediarix and Prevnar vaccines, and a second dose of the haemophilus influenza B vaccine. Pet'rs' Ex. 15 at 2.

On June 22, 2007, Petitioners took E.R. to the doctor due to seizure activity that began the previous night. Pet'rs' Ex. 4 at 73. E.R. was noted to have seizure activity at 7:30 PM, 12:30 AM, and again at 7:30 AM. *Id.* The child's seizure activity was described as "stiff and tense, [and] unresponsive," during which time his "face turned red" and his "eyes rolled into [the] back of [his] head." *Id.* The episodes of posturing that E.R. experienced looked "'like he had done a touchdown.'" *Id.* All episodes occurred within 30-45 minutes of consuming Tylenol, although he had taken Tylenol in the past without incident. *Id.* The notes from this visit also document a "[f]amily history of febrile seizures and malignant hyperthermia," but "no epilepsy history." *Id.* The assessment from this visit was "neuroleptic-induced acute dystonia,"[7] and the plan going forward was to switch E.R. from Tylenol to Motrin and observe him for further activity. *Id.* at 75. The visit notes further indicated that if E.R.'s seizure activity persisted or worsened, the doctor would start a seizure evaluation for a 6 month old; if the same, the doctor would wait "72 hours under the supposition that this [wa]s a vaccine reaction, which w[ould] be reported to the registry and cataloged as a relative contraindication to further immunization with pertussis component, the most likely culprit in neurologic events after 6 month immunizations." *Id.* at 75-76.

E.R. returned to the pediatrician on June 24, 2007, with a chief complaint of seizures. *Id.* at 71. The doctor provided the following assessment: "Neuroleptic-induced acute dystonia ? rare neurologic SE from DTAP vs pain response secondary to teething or early viral illness." *Id.* at 72. A neurology consultation was also scheduled on this day. *Id.*

E.R. returned to the pediatrician twice more, on June 25 and 28, 2007, for his "reaction to shots" and "post immunization" seizures, respectively. *Id.* at 64, 68. On the former date, Petitioners were given a medication instruction plan and told to treat the reflux with Zantac. *Id.*

[7] Dystonia is "dyskinetic movements due to disordered tonicity of muscle." Dystonia, *Dorland's*.

at 70. On the latter, Petitioners were told that E.R. had "gastroesophageal reflux." *Id.* at 67. Dr. Hill noted the possibility of "Sandifer's syndrome."[8] *Id.*

E.R. "was admitted to the hospital by Dr. Pollock [on June 28, 2007], after an EEG[9] performed by Dr. Bachman confirmed a diagnosis of hypsarrhythmia."[10] Pet'rs' Ex. 3 at 104. The diagnosis was "seizure disorder," and "infantile spasms." *Id.* E.R. was begun on ACTH.[11] *Id.* By "the end of his hospitalization," E.R. "seemed to be showing some early signs of response with the ACTH." *Id.* E.R. was discharged by Dr. Edwards on June 30, 2007 "to follow up with Cape Fear Pediatrics." *Id.*

On July 10, 2007, Dr. Duffy, a neurologist at Boston Children's Hospital, evaluated E.R. Pet'rs' Ex. 7 at 1. An EEG was conducted "on an urgent basis." *Id.* Dr. Duffy's impression of the EEG found it "suggestive of an underlying problem that is asymmetrical and by default [] may have represented an encephalopathic response to the immunizations." *Id.* E.R. was seen again by Dr. Duffy on July 19, 2007. *Id.* at 9. Dr. Duffy noted that the previous visit's EEG noted no presence of infantile spasms. *Id.* Dr. Duffy observed some improvement, as E.R. was not as irritable as before. *Id.*

Beginning on August 9, 2007, E.R. was evaluated by another neurologist, Dr. Weig. Pet'rs' Ex. 8 at 16-17. Dr. Weig noted, "the etiology of [E.R.'s] infantile spasms is not clear at this point. It certainly appears to be 'vaccine related' at least in a temporal sense, if not in a pathophysiologic one." *Id.* at 21. Dr. Weig indicated that a prognosis for E.R. was not definite, but that he "certainly is at high risk for ongoing developmental disabilities and seizures." *Id.*

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[8] Sandifer's syndrome "involves spasmodic torsional dystonia with arching of the back and rigid opisthotonic posturing, mainly involving the neck, back, and upper extremities, associated with symptomatic gastroesophageal reflux, esophagitis, or the presence of hiatal hernia." Pegeen Eslami, *Sandifer Syndrome: Overview*, Medscape (Nov. 11, 2015), http://emedicine.medscape.com/article/931761-overview.

[9] An EEG, or electroencephalogram, records "the potentials on the skull generated by currents emanating spontaneously from nerve cells in the brain." Electroencephalogram, *Dorland's*.

[10] Hypsarrhythmia is "an electro-encephalographic abnormality sometimes observed in infants, with random, high-voltage slow waves and spikes that arise from multiple foci and spread to all cortical areas." Hypsarrhythmia, *Dorland's*.

[11] ACTH refers to the adrenocorticotropic hormone. ACTH, *Dorland's*. The adrenocorticotropic hormone, also known as the adrenocorticotrophic or corticotrophic hormone, is one that has "a stimulating effect on the adrenal cortex." Adrenocorticotropic, *Dorland's*.

In January of 2008, E.R. began a ketogenic diet. Pet'rs' Ex. 9 at 83. An MRI of E.R.'s brain in February was normal, but his EEGs remained abnormal. *Id.* at 87-88, 90. In April, a treating physician, Dr. Thiele, observed that since starting the diet and his anticonvulsant medications, E.R.'s seizure control thereafter "improved dramatically." *Id.* at 84.

That being said, on July 16, 2010, physicians noted that an MRI showed "abnormal thickening of the cortex and loss of gray-white differentiation in the anterior right temporal lobe, involving the amygdala, parahippocampal gyrus, and inferior temporal gyrus." Pet'rs' Ex. 27 at 366. This, they explained, was "consistent" with a focal cortical dysplasia ("FCD").[12] Pet'rs' Ex. 27 at 366.

E.R. was hospitalized from October 13-18, 2010, for surgical removal of the FCD with a right temporal craniotomy and temporal lobectomy. Pet'rs' Ex. 35 at 1, 101; *see* Kabat & Król at 41 (explaining surgical treatment of FCD). Because the surgery was primarily performed using cauterization, little tissue was available for pathological examination. Tr. at 281-83, ECF No. 84.[13] Despite the surgery, E.R. continued to have seizures; but Petitioners reported progress in social engagement, feeding, and eating. Pet'rs' Ex. 36 at 3.

II. PROCEDURAL BACKGROUND

The petition was filed in this case on July 27, 2009, alleging that the DTaP vaccination caused E.R. to suffer encephalopathy and intractable seizures. Pet. at 1. The petition included a Motion for a Ruling on the Record pursuant to Rule 8 of the Vaccine Rules of the United States Court of Federal Claims, which governs summary judgment. *Id*. at 20-30. The case was originally assigned to Special Master Abell. *See* Notice of Assignment, ECF No. 2. Petitioners' counsel of record was Ronald Homer, Esq. Pet. at 30.

Respondent's Rule 4(c) Report was filed on October 26, 2009. Resp't's Report, ECF No. 7. In the report, Respondent asserted that Petitioners had failed to provide sufficient evidence regarding causation and requested that the case be dismissed. *Id.* at 8-9.

On November 9, 2009, a Rule 5 status conference was scheduled for January 19, 2010, to address Respondent's Rule 4(c) Report and Petitioners' Motion for a Ruling on the Record, which was construed as a partial motion for summary judgment. Rule 5 Order at 1-2, ECF No. 8. The special master ordered Petitioners to file an expert report, a *curriculum vitae* ("CV") of

[12] FCD is an umbrella term, forming "a very heterogenous group of cortical lesions." Joanna Kabat & Przemyslaw Król, *Focal cortical dysplasia – review*, 77 Polish J. Radiology 35, 36 (2012) (hereinafter "Kabat & Król").

[13] Unless specified otherwise, "Tr." refers to the transcript of the June 18, 2013 proceedings.

the opining expert, and any articles of medical literature relied upon in forming the expert opinion. *Id.* at 1.

On December 1, 2009, Petitioners filed a Renewed Motion for Partial Summary Judgment, alleging that the affidavit from E.R.'s mother, "the medical records, and the opinions of [E.R]'s treating physicians contained in those records, demonstrate by preponderant evidence that the DTaP vaccine, not something else, caused his injury." Notice (Dec. 1, 2009) at 6, ECF No. 9. Respondent thereafter filed a "Response to Renewed Motion for Partial Summary Judgment," *see* Resp. to Notice at 1, ECF No. 11, and a study from the Institute of Medicine ("IOM"), *see* Resp't's Ex. A, ECF No. 10-1 (excerpt from Comm. to Review the Adverse Consequences of Pertussis & Rubella Vaccines, Div. of Health Promotion & Disease Prevention, Inst. of Med., *Adverse Effects of Pertussis and Rubella Vaccines* (Christopher P. Howson et al. eds., 1991)). Respondent contended that "[P]etitioner[s] ha[d] not proven, nor does the current record establish, that the vaccinations at issue in this case *can cause* infantile spasms." Resp. to Notice at 2. Respondent quoted the aforementioned study, which concluded, "[t]he evidence does not indicate a causal relationship between DPT vaccine or the pertussis component of DPT and infantile spasms." *Id.* at 2-3 (internal quotation marks omitted). Respondent also asserted that Petitioners had "not proven in a case-specific manner that the DTaP vaccine *did cause* [E.R.'s] condition." *Id.* at 3.

On March 8, 2010, Petitioner filed a medical expert report from Paul Maertens, M.D., with supporting medical literature and his CV. Pet'rs' Exs. 18 and 19, ECF Nos. 15-1 to -10.

On March 30, 2010, pursuant to Vaccine Rule 3(c), the case was reassigned to Special Master Campbell-Smith. Order Reassigning Case, ECF No. 17. On May 21, 2010, Respondent submitted the expert report of Dr. Mary Anne Guggenheim, M.D., seven articles that Dr. Guggenheim relied upon in formulating her opinion, and Dr. Guggenheim's CV. Resp't's Exs. B and C, ECF Nos. 18-1 to -9.

On June 24, 2010, the parties appeared before Special Master Campbell-Smith for a status conference. Order (June 24, 2010) at 1, ECF No. 22. During that status conference, an evidentiary hearing was scheduled for November 3, 2010, in Boston, Massachusetts. *Id.* at 2.

On October 6, 2010, Respondent apprised the Court that E.R.'s "most recent MRI from June 16, 2010, showed, *inter alia*, '[a]bnormal cortical thickening . . . consistent with [FCD]' that was not evident on previous MRI's [sic]." Notice of Filing (Oct. 6, 2010) at 1, ECF No. 31 (quoting Pet'rs' Ex. 27 at 365). Respondent indicated that "[c]ortical dysplasia is a developmental malformation" and a "cause of infantile spasms." *Id.*

A status conference was held on October 28, 2010, at the request of the parties. Scheduling Order (Oct. 29, 2010) at 1, ECF No. 36. During the status conference, "Petitioner[s'] counsel noted that [E.R.] had recently undergone surgery for cortical dysplasia." *Id.* "In light of this recent hospitalization which suggests that a congenital causal factor might have been at play in the development of [E.R.]'s epilepsy," Petitioners' counsel argued, "it would be prudent to postpone the upcoming expert hearing." *Id.* Respondent's counsel agreed, and the entitlement hearing scheduled for November was canceled. *Id.*

A status conference was held on December 13, 2010, and the parties discussed the need for supplemental briefing following E.R.'s recent surgery for cortical dysplasia. Scheduling Order (Dec. 15, 2010) at 1, ECF No. 39. The parties were instructed to file supplemental reports from their experts, as informed by E.R.'s recent hospitalization, and deadlines were set. *Id.*

On July 28, 2011, Petitioners indicated that the case was receiving review by alternative counsel. Pet'rs' Mot. for Extension of Time (July 28, 2011) at 1, ECF No. 45. On August 25, 2011, Petitioners moved to substitute Anne C. Toale as the primary attorney for Petitioners. Mot. to Substitute Attorney, ECF No. 46. Petitioners' motion was granted. Unnumbered Order dated Aug. 25, 2011.

Petitioners did not ultimately file a supplemental report from Dr. Maertens. Instead, they filed the expert report and CV of Dr. Marcel Kinsbourne, M.D., on April 16, 2012. Pet'rs' Exs. 39-40, ECF Nos. 53-1 to -2. On September 25, 2012, Respondent filed the supplemental expert report of Dr. Guggenheim and the medical literature on which Dr. Guggenheim relied. Resp't's Ex. G, Tabs 1 to 5, ECF Nos. 62-1 to -6.

The parties conducted a status conference on October 17, 2012. Scheduling Order (Oct. 23, 2012) at 1, ECF No. 64. During the status conference, the parties agreed that an entitlement hearing would be held on June 18, 2013 in Washington, DC. *Id.* at 2.

Petitioners thereafter filed the supplemental expert report of Dr. Kinsbourne and all exhibits that Dr. Kinsbourne relied upon in this report. Pet'rs' Exs. 61-70, ECF Nos. 66-1 to -10.

On March 4, 2013, pursuant to Vaccine Rule 3(d), this case was reassigned to the undersigned. Order Reassigning Case, ECF No. 67. On March 22, 2013, Respondent filed the second supplemental expert report of Dr. Guggenheim and the medical literature that Dr. Guggenheim relied on in that report. Resp't's Ex. H, Tabs 1 to 7, ECF Nos. 68-1 to -8.

The parties filed pre-hearing memoranda on May 14 and 23, 2013, respectively. Pet'rs' Prehearing Submissions, ECF No. 75; Resp't's Prehearing Submissions, ECF No. 77. On June

4, 2013, Petitioners' counsel filed an affidavit identifying the reason for Dr. Maertens' withdrawal from this case.[14] Pet'rs' Ex. 80 at 4, ECF No. 79-1.

The entitlement hearing began on June 18, 2013. *See generally* Tr. On June 19, 2013, the undersigned postponed the remainder of the hearing because of a previously undisclosed potential conflict involving one of the attorneys. *See* Order (Aug. 14, 2013) at 5-7, ECF No. 85. On October 31, 2013, Petitioners' counsel moved to substitute attorney Edward Kraus in place of Anne Toale. Mot. to Substitute Attorney, ECF No. 95. The undersigned granted this request on November 6, 2013. Order (Nov. 6, 2013), ECF No. 97. The entitlement hearing was concluded on June 12, 2014, with Edward Kraus representing Petitioners, and Ryan Pyles representing Respondent. *See* Minute Entry dated June 12, 2014. Post-hearing briefing was completed October 3, 2014. *See* Pet'rs' Post Hr'g Br., ECF No. 104; Resp't's Post Hr'g Br., ECF No. 106.

III. LEGAL STANDARD

To receive compensation under the Program, Petitioners must prove either (1) that E.R. suffered a "Table Injury," i.e., an injury falling within the Vaccine Injury Table,[15] corresponding to one of his vaccinations, or (2) that E.R. suffered an injury that was actually caused by a vaccine. *See* 42 U.S.C. §§ 300aa-11(c)(1), 13(a)(1)(A) (2012). Petitioners must show that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly v. Sec'y of HHS*, 592 F.3d 1315, 1321-22 (Fed. Cir. 2010) (internal quotation marks omitted).

Because Petitioners do not allege a Table injury in this case, they must prove that E.R.'s injury was caused-in-fact by a covered vaccine. To do so, Petitioners must satisfy all prongs of the test established by the Federal Circuit in *Althen*. The *Althen* test requires Petitioners to set forth: " (1) a medical theory causally connecting the vaccination and the injury [("*Althen* Prong One")]; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury [("*Althen* Prong Two")]; and (3) a showing of a proximate temporal relationship between vaccination and injury [("*Althen* Prong Three")]." 418 F.3d at 1278. To establish

[14] Petitioners did not cite Dr. Maertens' report at hearing or in their pleadings, and the report was drafted before the existence of the FCD was known, which changed Petitioners' theory of the case. The undersigned did not rely on Dr. Maertens' report.

[15] The Vaccine Injury Table "lists the vaccines covered under the Act; describes each vaccine's compensable, adverse side effects; and indicates how soon after vaccination those side effects should first manifest themselves." *Bruesewitz v. Wyeth, LLC*, 562 U.S. 223, 228 (2011). "Claimants who show that a listed injury first manifested itself at the appropriate time are prima facie entitled to compensation." *Id.*

entitlement to compensation under the Program, Petitioners must establish each of the three prongs of *Althen* by a preponderance of the evidence. *Id.*

The preponderance of the evidence standard has been interpreted to mean that Petitioners must show that the fact to be proven is more likely than not. *Moberly*, 592 F.3d at 1322 n. 2. Proof of medical certainty is not required. *Bunting v. Sec'y of HHS*, 931 F.2d 867, 873 (Fed. Cir. 1991). "[T]he purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280.

In determining whether Petitioners are entitled to compensation, the undersigned will consider all relevant material contained in the record. 42 U.S.C. § 300aa-13(b)(1). That material can include circumstantial evidence. *Capizzano v. Sec'y of HHS*, 440 F.3d 1317, 1325 (Fed. Cir. 2006). As the finder of fact, the undersigned is "entitled--indeed, expected--to make determinations as to the reliability of the evidence presented . . . and, if appropriate, as to the credibility of the persons presenting that evidence." *Moberly*, 592 F.3d at 1326.

The Vaccine Act was created to award compensation to vaccine-injured persons "quickly, easily, and with certainty and generosity." *Graves v. Sec'y of HHS*, 109 Fed. Cl. 579, 595 (2013) (internal quotation marks omitted). Therefore, "close calls regarding causation are resolved in favor of injured" petitioners. *Althen*, 418 F.3d at 1280.

To satisfy the first prong of the *Althen* test, Petitioners must provide "a medical theory causally connecting the vaccination and the injury." *Althen*, 418 F.3d at 1278 (internal quotation marks omitted). Petitioners' theory must show that it is more likely than not that the vaccine E.R. received "can" cause the type of injury Petitioners allege the vaccine caused. *Pafford v. Sec'y of HHS*, 451 F.3d 1352, 1356 (Fed. Cir. 2006) (internal quotation marks omitted).

The medical theory set forth by Petitioners need only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of HHS*, 35 F.3d 543, 548-49 (Fed. Cir. 1994). When a petitioner proffers a medical opinion is proffered to support the theory alleged, the basis for the opinion and the reliability of that basis must be considered in determining how much weight to afford the offered opinion. *Broekelschen v. Sec'y of HHS*, 618 F.3d 1339, 1347 (Fed. Cir. 2010).

To satisfy the second prong of the *Althen* test, Petitioners must establish "'a logical sequence of cause and effect showing that the vaccination was the reason for the injury.'" *Althen*, 418 F.3d at 1278. That is, Petitioners must show, by preponderant evidence, that the vaccination E.R. received *did* cause the injuries Petitioners allege that it caused. *Capizzano v. Sec'y of HHS*, 440 F.3d 1317, 1326 (Fed. Cir. 2006). Petitioners may satisfy their burden by presenting circumstantial evidence and reliable medical opinions from treating physicians as well

as experts; they not required to offer "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." *Id.* at 1325-26. Ultimately, the "logical sequence of cause and effect must be informed by sound and reliable medical or scientific explanation." *Knudsen,* 35 F.3d at 548 (internal quotation marks omitted).

To satisfy the third prong of *Althen*, Petitioners must produce preponderant evidence of "a proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1278. This prong helps to establish the connection between the causal theory of Prong One and the more fact-based cause and effect arguments of Prong Two by demonstrating "that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *De Bazan v. Sec'y of HHS*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

If Petitioners satisfy all three prongs of *Althen* by a preponderance of the evidence, they establish a *prima facie* case. *Walther v. Sec'y of HHS*, 485 F.3d 1146, 1149 (Fed. Cir. 2007). After Petitioners have established a *prima facie* case, the burden shifts to Respondent to demonstrate, also by a preponderance of the evidence, that the injury was actually caused by factors unrelated to the administration of the vaccine. *Walther*, 485 F.3d at 1151. Accordingly, "[i]f the evidence is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded." *Knudsen*, 35 F.3d at 550.

IV. ANALYSIS

A. Background on Infantile Spasms

Infantile spasms refers to "a syndrome of severe myoclonus appearing in the first 18 months of life and associated with general cerebral deterioration; it is marked by severe flexion spasms of the head, neck, and trunk and extension of the limbs." Spasm, infantile, *Dorland's*. In addition to a condition, Dr. Kinsbourne described an infantile spasm as an event that "takes about a second in which the child does the following: the head drops, the arms fling up, the legs pull up." Tr. at 25. This, according to Dr. Kinsbourne, is sometimes called "jackknifing." *Id.* Dr. Kinsbourne stated that most children who suffer from infantile spasms begin with one event, with time, the events gather in "frequency and prominence." *Id*. at 26.

Dr. Guggenheim testified at hearing that West syndrome[16] and infantile spasms are synonymous. *Id.* at 226. Dr. Guggenheim further described infantile spasms as a "unique

[16] Dr. Guggenheim explained that "West syndrome is labeled so because it was first described in the mid-1800s by Dr. Benjamin West in England describing his own son." *Id*. at 226.

epilepsy." *Id*. Moreover, Dr. Guggenheim indicated, infantile spasms are specifically "characterized by the unique pattern of the seizures that the infant has because it's almost always under a year of age." *Id*. at 228. That "unique pattern," Dr. Guggenheim continued, consists of "brief events of either tonic or flexor spasms." *Id.*[17] The spasms also "tend to come in clusters," she explained, which "may be as few as two or three or as many as 50 or 100," but is typically "on the order of 10 or 20." *Id.* at 228-29. Infantile spasms have been described in children "as young as a month and as old as perhaps 18 months," she noted, "but 90 percent occur between four and eight months of age, with the peak being at six months." *Id.* at 229. Dr. Guggenheim also mentioned the unique EEG pattern[18] of those with infantile spasms, which can be described as a "hypsarrhythmia" that appears as very chaotic. *Id*. Dr. Kinsbourne explained that this means that "rhythms are lacking, or they're diminished, and at the same time, there are high amplitude waves, meaning excessive excitation." *Id.* at 29.

B. Qualifications of the Parties' Experts

1. Dr. Kinsbourne

Petitioners' expert, Dr. Marcel Kinsbourne, graduated from Oxford University in 1952 with a Bachelor of Arts degree. Pet'rs' Ex. 40 at 1. He attended Oxford University Medical School and graduated with the equivalent of a medical degree in 1955. *Id.*; *see* Tr. at 11. Dr. Kinsbourne also received a Master of Arts degree and a Doctor of Medicine degree from Oxford University. Pet'rs' Ex. 40 at 1.

Dr. Kinsbourne had nine years of post-graduate training in the areas of pediatrics, neurology, and pediatric neurology, at several hospitals and facilities in England and the United States. Tr. at 10-11; Pet'rs' Ex. 40 at 1. He has also been appointed to many academic positions. *See* Pet'rs' Ex. 40 at 2. Notably, he served as a University Lecturer in Experimental Psychology at Oxford University, from 1964 to 1967; as an Associate Professor in Pediatrics and Neurology at Duke University Medical Center, from 1967 to 1974; as a Professor of Psychology at the University of Waterloo, from 1974 to 1979; and as a Professor of Pediatrics at the University of Toronto, from 1974 to 1980. *Id.*

[17] Dr. Guggenheim clarified that "[t]onic is extension, flexor is flexion," and both "may involve virtually all of the body or some parts of the body." *Id.* In short, they are "asymmetric jerks." *Id.*

[18] Dr. Kinsbourne clarified that EEGs generally measure the brain's "mental processes," that is, "what it's doing, how it's working," by recording the different frequencies produced in different parts of the brain. *Id.* at 27, 30.

In 1980, Dr. Kinsbourne returned to the United States and served as Director of the Eunice Kennedy Shriver Center for Developmental Disabilities, Lecturer in Neurology at Harvard Medical School, and Clinical Associate in neurology at Massachusetts General Hospital, until 1991. *Id.* He then served as Director of the Behavioral Neurology Unit at Sargent College of Allied Health Professions at Boston University, from 1991 to 1992. *Id.* Currently, Dr. Kinsbourne is Professor of Psychology at New School University in New York. *Id.*

Dr. Kinsbourne also was awarded a Fulbright Traveling Scholarship, the Queens Prize in Neurology, the James Arthur Lectureship on Evolution of the Brain at the American Museum of Natural History, and the Visiting Resident Scholar Award from the Rockefeller Foundation. *Id.* He is licensed to practice medicine by the United Kingdom, the State of North Carolina, the Medical Council of Canada, the Commonwealth of Massachusetts, and the Commonwealth of Virginia. *Id.* at 1. He is a Member of the Royal College of Physicians and the American Board of Pediatrics. *Id.*

Dr. Kinsbourne has 373 publications listed under the "Bibliography" section of his CV. *See id.* at 5-35. Of note, Dr. Kinsbourne authored an article entitled, "Myoclonic Encephalopathy of Infants," which concerns the concept of a myoclonic disorder and how to diagnose and understand it. *Id.* at 25. Dr. Kinsbourne stated that "[n]owadays it's mostly called opsoclonus, which is a sudden jerking of the eyes, unwilled and unpredictable, and myoclonus syndrome or Kinsbourne's disease," named after Dr. Kinsbourne for his work on the disorder. Tr. at 15-16.

Dr. Kinsbourne was offered and admitted at hearing as an expert in pediatric neurology. Tr. at 22-24.

2. Dr. Guggenheim

Dr. Mary Anne Guggenheim attended Willamette University in Salem, Oregon from 1953 to 1957, and graduated with a Bachelor of Arts degree in Chemistry. Respt's' Ex. C at 1. She attended Harvard Medical School and graduated in 1964 with a degree in medicine. *Id.* She completed her post-graduate work at Cleveland Metropolitan General Hospital from 1964 to 1966, an NIH-NCI post-doctoral fellowship from 1966 to 1968 in virology research, and worked at St. Louis Children's Hospital in neurology and child neurology and at the University of Colorado Health Sciences Center in neurology and neuropathology. *Id.*

Dr. Guggenheim has been certified by the American Board of Pediatrics since 1972, and the American Board of Psychiatry and Neurology, with special competence in Child Neurology, since 1973. *Id.* She has been appointed as an Instructor in Pediatrics at Washington University School of Medicine, an Instructor in Pediatrics and Neurology at the University of Colorado

School of Medicine, a Professor and Clinical Professor in Pediatrics and Neurology at the University of Colorado School of Medicine, and an Adjunct Professor in the WAAMI Program in Bozeman, Montana, through the University of Washington School of Medicine. *Id.* at 2. Dr. Guggenheim indicated that she has "managed many children with infantile spasms." Tr. at 222.

Her appointments include serving on the Executive Committee of the Child Neurology Society from 1979 to 1983, including service as President from 1981 to 1982; she also served as Vice-Chairperson of the Department of Pediatrics at the University of Colorado School of Medicine. Pet'rs' Ex. 40 at 2.

Dr. Guggenheim was licensed to practice medicine in Colorado in 1971 and has been licensed in Montana since 1980. *Id.* at 1. She has 31 publications listed on her CV. *See id.* at 5-7.

Dr. Guggenheim was offered and admitted at hearing as an expert in pediatric neurology. Tr. at 223.

C. The Parties' Arguments

1. The Experts

i. Dr. Kinsbourne

The parties ultimately agree that E.R. suffered from an FCD, and that this fact predisposed him to seizure activity. Acknowledging this predisposition, Dr. Kinsbourne argues that the seizure activity would not have occurred in the absence of a triggering event, and that, in E.R.'s case, the triggering event was the DTaP vaccination. In his expert report and at hearing, Dr. Kinsbourne articulated the following position.

"[I]n this possibly unique case we have a child given an agent, namely, a vaccine, which is known to be capable of lowering seizure threshold on occasion," *id.*, specifically, the pertussis vaccine, which is a component of the DTaP vaccination, and which has been linked to seizures, albeit not to infantile spasms in particular. *Id.* at 121-22, 125. "[W]e have an area in that child's brain with really a lower seizure threshold, [the FCD,] so it seems . . . to be medically logical that in this particular case the seizure disorder was triggered by vaccine." *Id*. at 128. This could be called the "second hit" theory; that is, the first "hit" is the dysplasia itself, the second "hit" is the triggering event that causes the dysplasia to emit the signals that cause seizures—in this case, the pertussis vaccination. *See, e.g.*, Tr. at 111-12, 176-77.

Initially, "[v]accinations cause the release of proinflammatory cytokines, including interleukin-1 beta (IL-1 beta) as part of a reaction by the innate immune system that is a necessary antecedent for the stimulation of an adaptive immune response that will confer immunity." Pet'rs' Ex. 39 at 7 (citations omitted). In other words, vaccinations activate the immune system "towards a relatively benign challenge so as to resist the most severe challenge of the actual disease." Tr. at 132-33. The innate immune system works first, and then "enables a reaction by the adaptive immune system." *Id*. at 133. The innate immune system responds with inflammation which is local; it rallies "pro-inflammatory cytokines," which "are chemicals that actually jack up the likelihood of inflammation, and one aspect of the inflammation is the fever." *Id*. Subsequently, "[t]he pro-inflammatory cytokines initiate what's called a 'biochemical cascade.'" *Id*. at 134. One particular cytokine, interleukin-1 beta or IL-1 beta, is "the main agent in causing the fever which one gets when one has a variety of sicknesses." *Id*. IL-1 beta also has an effect on the hippocampus, "which is the particular area for generating seizures." *Id.*

Regarding seizure thresholds, there are two types of neurons which play a role in a seizure event, excitatory and inhibitory. *Id*. at 28. Neurons that have an excitatory effect "increase their rate of firing" when they project to other neurons. *Id.* Inhibitory neurons "decrease the rate of firing" when projected to other neurons. *Id*. "About 80 percent of the neurons in the forebrain are excitatory and about 20 percent are inhibitory." *Id.* Naturally, "it is necessary for the brain to keep the ratio of excitation and inhibition under control." *Id*. A seizure might be called a "disinhibitory excitation." *Id.* During a seizure, "the inhibition is insufficient and then the amount of synchronization and rapid firing goes and goes and goes and goes and then manifests itself in one or other of these ways." *Id.*

"The infant brain is more apt to have seizures" because "the excitatory neurons develop earlier than the inhibitory ones." *Id*. at 33. Put simply, the infant brain tends to have a "lower seizure threshold." *Id*. As well, the "circuits" in an infant are not "really hooked up with each other very much yet, so you don't see necessarily the coordinated rhythmic activities involving the whole body, which means that all the circuits are working together." *Id*. Infantile spasms typically appear from "about five or six months to about 18 months." *Id*.at 34.

With regard to E.R., in addition to having the low seizure threshold of infants, he suffered from an FCD (although this condition was not discovered until July 2010, when E.R was three-and-a-half years old, and the petition had been pending almost a year). *See supra* Parts I-II. Generally speaking, "a dysplasia is a condition caused by an abnormality in the development of the nervous system." Tr. at 62. It is an abnormality that occurs when the cells that will become the nervous system are migrating from the "neural chest" to the cerebral cortex. *Id.* at 62. This abnormality can be a lamination error, in which the cells end up in the wrong layer of the brain; a structural error, in which the neurons themselves are malformed; a cellularity abnormality (too many neurons, or too few); or a combination of the three. *Id.* at 65-66. One

reason that E.R.'s FCD may not have been seen in MRIs is due to indistinct boundaries in the brain. *Id*. at 34-35. Once a seizure happens, "the boundaries between the affected area, which is gray matter, and the unaffected base, which . . . is white matter, become[] distinct." *Id*. at 35. Dr. Duffy, one of Petitioner's physicians, commented on the abnormal finding by stating, "'[m]y impression of the EEG is that it is suggestive of an underlying problem that is assymetrical.'" *Id*. at 46 (quoting Pet'rs' Ex. 7 at 1). And "he noted it because it seemed that . . . towards the back of the right hemisphere [of the brain]" there was an "abnormal rhythm," which would signify "a tumor, an abscess, something that's generating the irritation of the nervous system which is causing the seizures." *Id*. Notably, Dr. Duffy went on to say, "'[i]t would be quite unusual for a full picture of infantile spasms, hypsarrhythmia, to begin so suddenly and dramatically unless there were a trigger event such as an immunization.'" *Id*. at 47 (quoting Pet'rs' Ex. 7 at 1-2). When an MRI was taken of E.R.'s brain in July 2010, it revealed "'abnormal thickening of cortex and loss of gray-white differentiation in the anterior right temporal lobe involving the amygdala, parahippocampal gyrus, and inferior temporal gyrus.'" *Id*. at 60 (quoting Pet'rs' Ex. 27 at 365). The thickening was described as a "microdysplasia." *Id*. at 61. After another MRI study, physicians confirmed that it was FCD. *Id.* at 61-62.

Thus, in sum, the medical community is well aware that dysplasias "have lower seizure thresholds than the rest of the cortical surface," such that "they're like a loaded gun waiting to discharge," and it is undisputed that E.R. had such a condition. *Id.* at 128. The relevant question, however, is "what discharges them," and the answer is "mostly" unknown. *Id.*

ii. Dr. Guggenheim

Respondent argues that a trigger is not necessary to prompt seizures in patients diagnosed with FCD. Respondent also argues that, even E.R.'s seizures were triggered by something other than FCD, that trigger was his infant brain maturation, not the DTaP vaccine. At hearing and in her expert report, Dr. Guggenheim argued as follows.

Generally, Petitioner's theory of vaccine causation does not satisfy any of the *Althen* prongs. "[A]lthough there was temporal proximity," Petitioner presented no "evidence to support the allegation that it either aggravated or to us[e] the word 'triggered' . . . in any way worsened, aggravated, uncovered the infantile spasms that [E.R.] presented with." *Id*. at 225-26. To be sure, "the term 'second hit' is used frequently these days in some literature relating to epileptogenesis." Pet'rs' Ex. H at 2. That being said, "the hypothesis that [E.R.]'s [infantile spasms] were 'triggered' by the vaccines, implying that without the immune stimulus his FCD would have been asymptomatic, is not supported by clinical or laboratory evidence." *Id*. As to whether the pertussis vaccination delivered a "second hit" to E.R.'s brain, there is no data or evidence that would lead one "to say that vaccines have any role in infantile spasms per se and in the course that this particular child has had and that most children with infantile spasms take."

Tr. at 291. "The general consensus [in the pediatric neurologist community] is that there is no evidence for any causative role" between vaccines and infantile spasms. *Id*. at 306.

Further, the medical literature suggested that there is no "need to invoke a second hit," as there is "considerable evidence that there is inherent epileptic -- epilepsy potential within the dysplastic tissue itself." Tr. (July 3, 2014) at 522, ECF No. 102. "[T]here are no clinical or laboratory studies to refute the current assumption held by the majority of child neurologists that when a child who develops [infantile spasms] has a FCD with demonstrated epileptogenicity, . . . the FCD is the underlying cause." Resp't's Ex. H at 4.

Admittedly, vaccinations have "been referenced by some people as being 'a cause' of temporal proximity" with regard to infantile spasms. Tr. at 234. Again, however, "the vast majority of people who work in pediatric neurology have come to the conclusion that in that circumstance, temporal proximity does not equate with causation simply because there's no proven underlying pathology of the brain." *Id*. Moreover, a study identifying over 200 potential causes of infantile spasms identified FCD as one, but not vaccinations. *Id.* (citing Resp't's Ex. B, Tab 1 at 13-19, ECF No. 18-2 (excerpt from James D. Frost, Jr. & Richard A. Hrachovy, *Infantile Spasms: Diagnosis, Management, and Prognosis*, at 112-18 (2003)) (hereinafter "Frost & Hrachovy" with pincites to internal pagination)).

2. Post-Hearing Briefs

i. Petitioners

Petitioners contend that they have satisfied their burden under all three of *Althen*'s prongs by a preponderance of the evidence. Pet'rs' Post Hr'g Br. at 1-2. Initially, Petitioners emphasize that "'the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body.'" *Id.* at 2-3 (quoting *Althen*, 418 F.3d at 1280).

Petitioners first assert that, through Dr. Kinsbourne's testimony, they have articulated a plausible and reliable theory of how the DTaP vaccination could cause infantile spasms. *Id.* at 2-8. As to Respondent, Petitioners argue that she merely impugns the credibility of Dr. Kinsbourne, ignores the supporting literature, and cites epidemiological evidence in cases of children without FCDs. *Id.* at 3. To the contrary, Petitioners counter, Dr. Kinsbourne has a "long and distinguished career" as a pediatric neurologist and vaccine expert, as evidenced by his impressive qualifications. *Id.* at 3-4. Further, the medical literature supports his theory, Petitioners claim, because (1) "the pertussis vaccine causes the release of pro-inflammatory cytokines, in particular IL 1-beta," *id.* at 4; and (2) "an FCD in the cerebral cortex is a risk factor for epilepsy," as it lowers the seizure threshold, *id*. at 5; yet (3) "an individual with an FCD is not

predestined to develop epilepsy or for developing seizure activity at a particular time." *Id.* at 5-6. In addition, Petitioners contend that Respondent's data, which allegedly debunks the purported link between the DTaP vaccine and infantile spasms, is out of date, general in nature, and merely notes the absence of an observed relationship,[19] not the nonexistence of one. *Id.* at 7.

Petitioners also argue that there is a logical sequence of cause and effect linking the DTaP vaccine and E.R.'s infantile spasms. *Id.* at 8-11. Petitioners note that there are no disputes as to E.R.'s medical records, which paint a picture compatible with their theory of causation. *Id.* at 8-9. Although Respondent claims that it was E.R.'s FCD that was responsible for the infantile spasms, Petitioners retort that E.R. had, at most, a type one FCD, which would not normally present in the extreme fashion as it did here without aggravation. *Id.* at 10. While Dr. Guggenheim stated that E.R.'s brain tissue was insufficient to draw pathologic findings, i.e., to conclude that E.R.'s FCD was a type one, Petitioners contend that her testimony on this subject is not persuasive, as she is not credentialed in this area of medicine. *Id.* at 10-11.

Finally, Petitioners assert that the manifestation of onset of E.R.'s infantile spasms was temporally consistent with their theory of causation. *Id.* at 11-12. Notably, Petitioners point out, Dr. Kinsbourne explained that "the mechanism of the vaccine triggering seizure activity in E.R. involves a production of pro-inflammatory cytokines, including IL-1 beta, a process/reaction that is understood to generate fever and which occurs within hours or days of vaccination." *Id.* at 11. As to Respondent's evidence to the contrary, Petitioners explain that it "excluded cases, like E.R.'s, which involved a cerebral malformation." *Id.* at 12.

ii. Respondent

Generally, Respondent argues that "the evidence militates against the conclusion that vaccination substantially contributes to infantile spasms." Resp't's Post Hr'g Br. at 9. In any event, Respondent continues, E.R.'s "cortical dysplasia is sufficiently explanatory as the preponderant cause of his infantile spasms, such that the invocation of vaccination as causally related is purely speculative." *Id.* at 10.

Respondent first disputes the credibility and reliability of Dr. Kinsbourne. *Id.* at 10-12. In particular, Respondent asserts that "his attribution of vaccination causation" was based "on little more than a mere possibility, lacking the necessary indicia of reliability," and that his experience no longer extends to seizure cases, as he has not evaluated an epilepsy patient since 1980. *Id.* at 11. Respondent also points out that "Dr. Kinsbourne has historically invoked vaccines as causing seizure disorders." *Id.* at 17.

[19] Petitioners also point out that children with FCDs have a "rare" condition that puts them in a "high risk group" for developing infantile spasms; accordingly, general epidemiological studies would not accurately represent the relationship between *that* group and the DTaP vaccination.

Even accepting the credibility of Dr. Kinsbourne, Respondent argues, his theory of causation is not reliable. *Id.* at 12-22. At the outset, she notes that "the scientific community's understanding of the basic mechanisms of infantile spasms is unfortunately nascent," and that "not a single other credentialed person has even hypothesized that vaccines substantially contribute to infantile spasms." *Id.* at 12. As to the theory itself, Respondent claims that it is "rife with gaps," including the lack of a link between the acellular pertussis vaccine and seizure disorders, or between fever from cytokine IL-1 beta and infantile spasms (despite its connection with benign febrile seizures). *Id.* at 13. Respondent also criticizes the "second hit" theory as "working backwards in an attempt to shoehorn literature fragments into [Dr. Kinsbourne's] preordained conclusion of vaccine causation"; an attempt, she says, which has been rejected by at least one other special master. *Id.* at 15-17 (citing *Conway v. Sec'y of HHS*, No. 07-857V, 2011 WL 1167632, at *10, 12 (Fed. Cl. Spec. Mstr. Mar. 7, 2011)). Furthermore, Respondent asserts that Dr. Kinsbourne's theory ignores the weight of medical evidence discounting any purported link between vaccinations and infantile spasms, *see id.* at 18-19, as well as the distinction between infantile spasms and other seizure disorders, *see id.* at 19. Respondent also points out that Dr. Kinsbourne admitted that "the natural maturation of the brain at about the six-month mark is at least an equally valid explanation of why an underlying predisposition for infantile spasms might be 'triggered.'" *Id.* at 21 (citing Tr. at 167). Finally, Respondent contends that Petitioners have attempted to shift the burden of proof by arguing that Respondent has not offered epidemiological evidence that specifically refutes Dr. Kinsbourne's theory, when, in reality, Petitioners have offered no evidence in support of the theory. *Id.* at 22.

Because Petitioners' theory is invalid, Respondent continues, there can be no logical sequence of cause and effect between the vaccine and the infantile spasms in this case. *Id.* at 22-24. Nevertheless, Respondent singles out Dr. Duffy for criticism, claiming that his impression was based on insufficient information and contrary to that of other treating physicians. *Id.* at 23-24. Moreover, Respondent asserts, the medical records indicate that E.R. suffered from acute irritability and gnawing before the DTaP vaccine, Dr. Kinsbourne admitted the possibility that "such symptomatology could have represented a different 'second hit' to cause infantile spasms," and "infantile spasms often has an insidious onset," *id.* at 24 (citing Tr. at 161, 202, 236-37); thus, the manifestation of onset of E.R.'s infantile spasms most likely occurred before the vaccination.

Finally, Respondent contends that Petitioners' timeline is inconsistent with the medical literature because, typically, "there is a latency period of some months" between the onset of infantile spasms and its cause. *Id.* at 24. While acknowledging Petitioners' claim that this literature does not specifically address the second-hit theory, Respondent asserts that the second-hit theory is invalid in the first instance. *Id.* at 25.

D. The Undersigned's Decision

As Respondent notes, "the scientific community's understanding of the basic mechanisms of infantile spasms is unfortunately nascent." *Id*. at 12. Both parties were handicapped by this lack of scientific knowledge, as was the undersigned, who nonetheless must make a decision based on the evidence in the record.

Much of the causation evidence presented in this case proved to be irrelevant–once it became known that E.R. had an FCD, the causation analysis came down to two narrow and separate, but related, questions, both of which fall under *Althen*'s first prong. First, are infantile spasms inevitable in an individual with an FCD, or might the FCD need some sort of insult to trigger it into seizure activity? Second, if an insult is necessary in some situations, can the acellular pertussis vaccine act as that insult?

Respondent argued strongly in favor of inevitability. Dr. Guggenheim testified, "I don't think there's any need to invoke a second hit. I think there's considerable evidence that there is inherent epileptic -- epilepsy potential with the dysplastic tissue itself." Tr. at 522. And Dr. Kinsbourne agreed that dysplasias "are known to have lower seizure thresholds than the rest of the cortical surface . . . [t]hey're like a loaded gun waiting to discharge." *Id*. at 128.

However, Petitioners put forward several medical articles, including the Tezer-Filik article, *see* Pet'rs' Ex. 58 (Irsel Tezer-Filik et al., *A case with an asymptomatic malformation of cortical development diagnosed in eighth decade of life*, 111 Bratisi Lek Listy 467 (2010)), and the Kasper article, *see* Pet'rs' Ex. 64 (Burkhard S. Kasper et al., *Temporal Lobe Microdysgenesis in Epilepsy Versus Control Brains*, 58 J. Neuropathology & Experimental Neurology 22 (1999)), that demonstrate that a significant proportion of the population has some form of gross cortical dysgenesis without suffering any episodes of epilepsy. *See* Tr. at 114-18 (discussing articles); *see also* Pet'rs' Ex. 55 (Imad M. Najm et al., *Pathophysiological Mechanisms of Focal Corticol Dysplasia: A Critical Review of Human Tissue Studies and Animal Models*, 48 Epilepsia 21, n.16 (2007)) (hereinafter "Najm") ("[M]uch evidence has suggested to many that not all dysplastic lesions are epileptic."). Thus, at least in those individuals, infantile spasms or another form of epilepsy was not an inevitable consequence of suffering from a cortical dysplasia. As Dr. Kinsbourne put it, "it would seem that a lot of people with a similar dysplasia [to that of E.R.] had lived a normal nonepileptic life." *Id*. at 118. Beyond asserting that an FCD is inherently epileptic, Respondent had no explanation for why some individuals with cortical dysplasias do not develop infantile spasms, or develop epilepsy much later in life. Scientists have begun to study this phenomenon, but they have not gotten beyond theorizing that a "second hit" may be necessary to transform a "dormant" cortical dysplasia into an epileptic one, *see* Najm at 6, and beginning to examine what mechanisms may underlie that transformation. *Id*.

In sum, the evidence that dysplastic tissue has epilepsy potential, coupled with the proof adduced by Petitioners that at least some individuals with cortical dysplasias survive infancy without experiencing infantile spasms, demonstrates to the undersigned that some insult is necessary in some cases to trigger that inherent potential into the actuality of infantile spasms.[20]

This leads to the second question in this case: could a vaccine, specifically the pertussis vaccine, constitute that transformational mechanism? Petitioners assert that it can, and that it did in this case. Petitioners offered unrefuted evidence linking the pertussis component of the DTaP vaccine and seizures, *see supra* Part IV-C-1, and that the toxoiding[21] process was imperfect in the formulation of the pertussis vaccine. Tr. at 184-85. Respondent fervently argued that there is no evidence linking vaccinations and infantile spasms. In support, Respondent pointed to both an IOM report, which concluded that the evidence that acellular pertussis vaccine causes infantile spasms or seizures in normal children is inconclusive, *see* Pet'rs' Ex. I at 6, ECF No. 76-1 (excerpt from Comm. to Review Adverse Effects of Vaccines, Board on Population Health and Public Health Practice, Inst. of Med., *Adverse Effects of Vaccines: Evidence and Causality*, at 539 (Kathleen Stratton et al., eds., 2011)) (hereinafter "IOM Report"), and the Frost & Hrachovy study, which omitted vaccinations from its comprehensive list of potential causes of infantile spasms, *see* Frost & Hrachovy at 112-18. But the undersigned finds that the former's conclusion was based on only one epidemiological study and two small mechanistic studies, that it is not clear that the one epidemiological study was designed to assess the acellular pertussis component of the vaccine, and that the studies did not address the effect of the vaccine on children with a lowered seizure threshold, such as those with a fever. *See* IOM Report at 537-38. As to the latter, the undersigned makes two observations: (1) the absence of vaccinations from the study does not rebut the existence of a relationship, and (2) the fact that so many potential causes of infantile spasms exist indicates, as previously noted, a certain ignorance of the true origin of the condition. In sum, despite the relative dearth of information concerning the causes

[20] There was a great deal of discussion in expert reports and at hearing about the classification of FCDs according to their severity and structural features and how prone they are to cause epilepsy. *See, e.g.*, Najm; Pet'rs' Ex. 74 (Ingmar Blümcke et al., *Malformations of corticol development and epilepsies: neuropathological findings with emphasis on focal corticoal dysplasia*, 11 Epileptic Disorders 181 (2009)); Tr. at 74-75, 118, 303. Ultimately, this discussion proved irrelevant to the undersigned's decision for two reasons. First, there was not enough tissue left after E.R.'s surgery to facilitate an accurate classification. Second, as discussed previously, both experts agreed that the source of E.R.'s seizures was the FCD. The issue was whether the vaccine pushed the FCD into seizure activity, or whether it went there on its own. The pathology, unfortunately, was inadequate to assist in the resolution of that question.

[21] A toxoid is "a modified or inactivated bacterial exotoxin that has lost toxicity but retains the properties of combining with, or stimulating the formation of, antitoxin." *Dorland's*, Toxoid.

and mechanisms of infantile spasms and FCDs, the undersigned concludes that Petitioners have shown, by a preponderance of the evidence, that an FCD needs a "second hit" to become epileptic in some cases, and that the pertussis component of the DTaP vaccine can act as that second hit. Petitioners have thus met their burden of proof under *Althen*'s Prong One.

As to Prongs Two and Three of *Althen*, there is no dispute that E.R. had an FCD, and despite the lack of pathology, no dispute, ultimately, that the FCD was epileptogenic. There is no dispute that E.R. received the Pediarix vaccine containing the pertussis component, and that he developed infantile spasms within a few hours of that vaccination. E.R.'s pediatrician noted the reason for his repeated visits to be "post-immunization" seizures, after stating that E.R.'s reaction would be "catalogued as a relative contra-indication to further immunization with pertussis component, the most likely culprit in neurologic events after 6 month immunizations." Pet'r's Ex. 4 at 75-76. Neurologist Dr. Duffy evaluated E.R.'s EEG and found it "suggestive of an underlying problem that is asymmetrical." Pet'r's Ex. 7 at 1. Respondent discounted Dr. Duffy's assertion of a vaccine connection, and suggested that the asymmetry that Dr. Duffy observed was actually the foreshadowing of the yet undiscovered FCD and not a vaccine reaction. But, in response to the undersigned's questions on this point, Dr. Kinsbourne testified that this connection was

> absolutely what [Dr. Duffy] was suspecting – one of the manifestations of what he was suspecting in general would indeed be the dysplasia, but he was looking for an acute process. The dysplasia is not an acute process. So applying it to the dysplasia, he was looking for an acute aggravation of the dysplasia by a vaccine reaction.

Tr. at 190. In light of this evidence, the undersigned concludes that Petitioners have shown, by a preponderance of the evidence that, under the unique circumstances of this case, the DTaP vaccine was the second hit that drove E.R., who was predisposed to develop the condition due to his FCD, into infantile spasms.[22] Petitioners have also met their burden of proof under Prongs Two and Three of *Althen*, and are entitled to a Program award.

V. CONCLUSION

For the reasons set forth above, the undersigned finds that Petitioners have shown by medical records and competent medical opinion that E.R.'s medical condition was "more likely

[22] The undersigned emphasizes that her conclusion is narrowly circumscribed to the facts presented in this case. She makes no observations about the link between the Pediarix, DTaP, or acellular pertussis vaccines and infantile spasms, generally; rather, the undersigned merely observes that Petitioners have met their burden of proof under *Althen*'s first prong.

than not" vaccine-caused, and that he is entitled to compensation. This case is now ready to proceed to damages.

IT IS SO ORDERED.

/s/ Lisa D. Hamilton-Fieldman
Lisa D. Hamilton-Fieldman
Special Master